AO 440 (Rev. 12/09) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

District of Columbia

Noven Therapeutics, LLC.

Plaintiff

v.

The Honorable David J. Kappos

Defendant

Case: 1:11-cv-00607
Assigned To : Walton, Reggie B.
Assign. Date : 3/23/2011
Description: General Civil

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* United States Attorney for the District of Columbia
501 3rd Street, NW
Civil Division, 4th Floor
Washington DC 20536

A lawsuit has been filed against you.

Within ~~21~~ days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

Clarence Edward Polk, Jr.
Foley & Lardner, LLP
3000 K Street, N.W.
Washington, DC 20007

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

CLERK OF COURT

Date: MARCH 23, 2011

Maureen Higgins
Signature of Clerk or Deputy Clerk

RECEIVED
3/29/11
GN

Civil Action No.

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____
was received by me on *(date)* _____.

☐ I personally served the summons on the individual at *(place)* _____
_____ on *(date)* _____ ; or

☐ I left the summons at the individual's residence or usual place of abode with *(name)* _____
_____, a person of suitable age and discretion who resides there,
on *(date)* _____, and mailed a copy to the individual's last known address; or

☐ I served the summons on *(name of individual)* _____, who is
designated by law to accept service of process on behalf of *(name of organization)* _____
_____ on *(date)* _____ ; or

☐ I returned the summons unexecuted because _____ ; or

☐ Other *(specify)*:

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

_____
Server's signature

_____
Printed name and title

_____
Server's address

Additional information regarding attempted service, etc:

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVEN THERAPEUTICS, LLC
11960 SW 144th Street
Miami, FL 33186

Plaintiff,

v.

HON. DAVID J. KAPPOS
Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
Madison Building
600 Dulany Street
Alexandria, VA 22314

Defendant.

Case: 1:11-cv-00607
Assigned To : Walton, Reggie B.
Assign. Date : 3/23/2011
Description: General Civil

COMPLAINT

Plaintiff Noven Therapeutics, LLC ("Plaintiff"), for its Complaint against Defendant, the Honorable David J. Kappos, states as follows:

1. This is an action by the owner of United States Patent No. 7,598,271 ("the '271 patent") seeking review of inaccurate and erroneous patent term adjustment calculations made by the United States Patent & Trademark Office ("PTO"). Specifically, this is an action by Plaintiff seeking a judgment that the patent term adjustment of 2073 days calculated by the PTO for the '271 patent is erroneous and should be corrected as alternatively reflected in attached Exhibit A, to 2729 days or 2730 days.

2. This action arises under 35 U.S.C. § 154, the Administrative Procedure Act (5 U.S.C. §§ 701-706), and the Fifth Amendment to the Constitution of the United States.

I. THE PARTIES

3. Plaintiff Noven Therapeutics, LLC ("Noven Therapeutics") is a limited liability corporation organized under the laws of the state of Delaware.

4. Defendant David J. Kappos is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office. Defendant is sued in his official capacity. Defendant is the head of the PTO and is responsible for superintending or performing all duties required by law with respect to the granting and issuing of patents, and is designated by statute as the official responsible for determining the period for patent term adjustments under 35 U.S.C. § 154(b)(3)(B).

II. JURISDICTION AND VENUE

5. This Court has jurisdiction over this action and is authorized to issue the requested relief to Plaintiff pursuant to 28 U.S.C. §§ 1331, 1338(a), 1361, 2201 and 2202; 35 U.S.C. § 154(b)(4)(A), and/or 5 U.S.C. §§ 701-706.

6. Venue is proper in this district pursuant to 35 U.S.C. § 154(b)(4)(A), 28 U.S.C. § 1391(e) and/or 5 U.S.C. §§ 702-703.

7. This Complaint is timely filed, *inter alia*, in accordance with 35 U.S.C. § 154(b)(4)(A) and, alternatively, pursuant to 28 U.S.C. § 2401(a), and/or the doctrine of equitable tolling.

III. BACKGROUND

8. The '271 patent, attached as Exhibit B, issued on October, 6, 2009 to Noven Therapeutics, LLC, from U.S. patent application number 09/200,743, which was filed on November 30, 1998, by Synthon B.V. ("Applicant").

9. The '271 patent is not subject to a terminal disclaimer. Although a terminal disclaimer was filed during prosecution, a petition to withdraw the terminal disclaimer was granted on April 16, 2008.

10. Plaintiff Noven Therapeutics, LLC is the assignee of the '271 patent, and is the real party in interest in this case.

11. The Patent Term Guarantee Act of 1999, a part of the American Inventors Protection Act, amended 35 U.S.C. § 154(b) to address concerns that delays by the PTO during prosecution of patent applications could result in shortening the effective terms of patents, which are measured from their respective filing dates.

12. As amended, 35 U.S.C. § 154(b) guarantees patent term against three types of PTO delay: (A) the failure of the PTO to take action within certain time periods is addressed under 35 U.S.C. § 154(b)(1)(A); (B) the failure of the PTO to issue a patent within 3 years of its actual filing date is addressed under 35 U.S.C. § 154(b)(1)(B); and (C) delays due to interferences, secrecy orders and appeals are addressed under 35 U.S.C. § 154(b)(1)(C).

13. As set forth in 35 U.S.C. § 154(b)(1)(A), delays by the PTO require that "the term of the patent shall be extended 1 day for each day after the end of the period specified in clause (i), (ii), (iii), or (iv), as the case may be, until the action described in such clause is taken."

14. Under 35 U.S.C. § 154(b)(1)(A)(ii), an applicant is entitled to patent term adjustment when the PTO fails to "respond to a reply under section 132, or to an appeal taken under section 134, within 4 months after the date on which the reply was filed or the appeal was taken."

15. Under 37 C.F.R. § 1.703(a)(2), the PTO calculates that period of adjustment under 37 C.F.R. §1.702(a)(2) (corresponding to 35 U.S.C. § 154(b)(1)(A)(ii)) as "[t]he number of days, if any, in the period beginning on the day after the date that is four months after the date a reply under § 1.111 was filed and ending on the date of mailing of either an action under 35 U.S.C. 132, or a notice of allowance under 35 U.S.C. 151, whichever occurs first."

16. Under 35 U.S.C. § 154(b)(1)(A)(iv), an applicant is entitled to patent term adjustment when the PTO fails to "issue a patent within 4 months after the date on which the issue fee was paid under section 151 and all outstanding requirements were satisfied."

17. As set forth in 35 U.S.C. § 154(b)(1)(B), if the PTO fails to issue a patent within 3 years after the actual filing date, "the term of the patent shall be extended 1 day for each day after the end of that 3-year period." Under 35 U.S.C. § 154(b)(1)(B)(i), this extension shall not include time consumed by continued examination of the application requested by the applicant.

18. As set forth in 35 U.S.C. § 154(b)(1)(C), for delays due to an interference proceeding under 35 U.S.C. § 135(a), "the term of the patent shall be extended 1 day for each day of the pendency of the proceeding."

19. As set forth in 37 C.F.R. §1.703(c)(1), the PTO calculates that period of adjustment under 37 C.F.R. §1.702(c) ("Delays caused by interference proceedings") (corresponding to 35 U.S.C. § 154(b)(1)(C)) as including "[t]he number of days . . . in the period beginning on the date an interference was declared . . . and ending on the date that the interference was terminated." As set forth in 37 C.F.R. § 41.205(a), "After a final decision is entered by the Board, an interference is considered terminated when no appeal (35 U.S.C. 141) or other review (35 U.S.C. 146) has been or can be taken or had." 35 U.S.C. § 142 sets a minimum 60 day

period for an appeal to the Federal Circuit (e.g., 35 U.S.C. § 141) and 35 U.S.C. § 146 sets a minimum 60 day period for a civil action.

20. Any patent term adjustment due for PTO delays under 35 U.S.C. § 154(b)(1) is limited by 35 U.S.C. § 154(b)(2), which requires in 35 U.S.C. § 154(b)(2)(A) that the PTO take into account any overlap in the PTO delays, and which also requires that the PTO take into account any applicant delays under 35 U.S.C. § 154(b)(2)(C).

21. On November 27, 2000, Applicant filed a Continued Prosecution Application ("CPA") in connection with U.S. patent application number 09/200,743. The filing date of the CPA is treated as the filing date of the application for PTA purposes. *See* 37 C.F.R. § 1.53(d)(2).

22. On April 26, 2001, the PTO issued a Restriction Requirement to which Applicant filed a Response that was received at the PTO on May 31, 2001.

23. On August 2, 2001, the PTO issued a Notice stating that the patent application claims were "allowable" but "due to a potential interference, *ex parte* prosecution is suspended." The cover page of this paper erroneously refers to a "request for suspension of action under 37 C.F.R. § 1.103." Applicant filed a paper received at the PTO on August 3, 2010 clarifying that "the suspension was not requested by the applicants and is instead an action imposed by the USPTO under 37 C.F.R. § 1.103(e)."

24. The August 2, 2001 Notice did not include a rejection, objection or requirement to which Applicant was required to reply in order to continue prosecution. Indeed, as stated in the Notice, prosecution was "suspended."

25. The next communication issued by the PTO was the Declaration of Interference issued on October 1, 2002.

26. The Board issued a Decision in the interference proceeding in favor of Applicant on May 25, 2004, which was 603 days after the interference had been declared.

27. The interference proceeding was terminated 60 days later, when neither Applicant nor any other party filed an appeal from, or sought other review of, the Board Decision under 35 U.S.C. § 141 or 35 U.S.C. § 146. *See* 37 C.F.R. § 41.205(a).

28. The PTO issued a Notice of Allowance and Fee(s) Due on September 19, 2008, requiring that the issue fee be paid by December 19, 2008.

29. The September 19, 2008 Notice of Allowance indicated that "3148 day(s)" of PTA had been accrued to date.

30. Plaintiff believed that the 3148 days PTA indicated in the September 19, 2008 Notice of Allowance resulted from adding 2546 days PTO delay under 35 U.S.C. § 154(b)(1)(A) (the number of days from four months after the Response to the Restriction Requirement to the day the Notice of Allowance was mailed) and 602 days PTO delay under 35 U.S.C. § 154(b)(1)(A) (one day less than the number of days from the Declaration of Interference to the Board Decision in the interference), but did not account for the overlap between these periods of PTO delay, as set forth in 35 U.S.C. § 154(b)(2)(A). Thus, along with the issue fee payment, Plaintiff submitted a Communication Regarding Patent Term Adjustment noting that the PTO's calculation of 3148 days PTA did not agree with its own calculation of PTA and asking that the PTO "verify the calculation of Patent Term Adjustment."

31. Plaintiff paid the issue fee on October 1, 2008, thereby satisfying all outstanding requirements for grant of the patent.

32. In a Letter issued February 10, 2009, the PTO indicated that the PTA accrued to date had been recalculated as 2057 days. The PTO explained that 1455 days PTO delay was being awarded for the number of days from four months after the Board Decision in the interference to the day the Notice of Allowance was mailed. The PTO did not explain why PTA was not being awarded from the time period beginning four months after the Response to the Restriction Requirement was filed. The PTA Calculation sheet attached to the Letter indicated that 602 days PTO delay still were being awarded for the interference.

33. The PTO issued an Issue Notification indicating that the patent was set to issue on March 17, 2009, and would be awarded at total of 2101 days PTA. Plaintiff believed that the additional PTA was being awarded under 35 U.S.C. § 154(b)(1)(A)(iv), due to the PTO's failure to issue the patent within four months of the issue fee payment.

34. By March 6, 2009, 4 months and 33 days after Plaintiff paid the issue fee, the PTO had not yet issued the patent.

35. On March 6, 2009, Plaintiff filed a Petition to Withdraw Application from Issue (classified by the PTO as a "Request for Deferral of Issuance") along with a Request for Continued Examination in order to file an additional Information Disclosure Statement and related documents.

36. The PTO issued a second Notice of Allowance on April 17, 2009.

37. The April 17, 2009 Notice of Allowance indicated that "2057 day(s)" of PTA had been accrued to date.

38. Plaintiff believed that the 2057 days PTA indicated in the April 17, 2009 Notice of Allowance was based on the PTO's PTA Calculation provided with the February 10, 2009

Letter. Thus, along with the issue fee payment on May 21, 2009, Plaintiff filed a Request for Reconsideration of Patent Term Adjustment seeking the original award of 2546 days PTO delay under 35 U.S.C. § 154(b)(1)(A) (the number of days from four months after the Response to the Restriction Requirement to the day the Notice of Allowance was mailed) and seeking additional PTA under 35 U.S.C. § 154(b)(1)(B) in view of the decision of this Court in *Wyeth v. Kappos*, Civ. Action No. 07-1492 (JR) (Sep. 30, 2008).

39. Plaintiff paid the outstanding Issue Fee on May 21, 2009, thereby once again satisfying all outstanding requirements for grant of the patent.

40. In a Paper issued August 26, 2009, the PTO stated that the Request for Reconsideration of Patent Term Adjustment was "dismissed" as premature, in as much as it related to PTA due under 35 U.S.C. § 154(b)(1)(B), and "dismissed" as "not well taken" in as much as it related to PTA due under 35 U.S.C. § 154(b)(1)(A), because the PTO's August 2, 2001 Notice allegedly was "a notification under 35 U.S.C. 132."

41. The '271 patent issued on October 6, 2009, 4 months and 15 days after the issue fee was paid on May 21, 2009, with a total PTA award of 2072 days.

42. On October 22, 2009, within two months of the PTO's August 26, 2009 Paper and within two months of the October 6, 2009 grant date of the patent, Plaintiff filed a "Renewed Request for Reconsideration of PTA." Plaintiff again sought the original award of 2546 days PTO delay under 35 U.S.C. § 154(b)(1)(A) (the number of days from four months after the Response to the Restriction Requirement to the day the Notice of Allowance was mailed), and explained that the PTO's August 2, 2001 Notice could not be "a notification under 35 U.S.C. 132." Plaintiff also again sought additional PTA under 35 U.S.C. § 154(b)(1)(B), again citing this Court's decision in *Wyeth v. Kappos*. Plaintiff also explained that the PTO delay accrued

under 35 U.S.C. § 154(b)(1)(C) for the interference proceeding should be 603 days, but noted that the time period at issue overlapped with other time periods of PTO delay.

43. On June 2, 2010, Plaintiff filed a "Supplemental Renewed Request for Reconsideration of PTA" to note that the PTO had indicated that it would follow the Federal Circuit decision that affirmed this Court's decision in *Wyeth v. Kappos*.

44. On January 24, 2011, the PTO issued a "Decision" on Plaintiff's requests for reconsideration of PTA filed on October 22, 2009 and supplemented on June 2, 2010. The Decision identified five periods in dispute and granted one additional day PTA under 35 U.S.C. § 154(b)(1)(C), thereby bringing the total PTA award to 2073 days. In particular, the Decision indicates that the PTO is awarding (i) 603 days for the interference under 35 USC § 154(b)(1)(C); (ii) 1925 days for "three year delay" under 35 USC § 154(b)(1)(B), and (iii) 1455 days for "prosecution delay," apparently under 35 USC § 154(b)(1)(A)(iii), relating to the PTO's delays after the interference was decided. The PTO also has awarded (iv) 15 days PTA for delay in issuing the patent under 35 USC § 154(b)(1)(A)(iv), which is not in dispute and so is not mentioned in the Decision, but is taken into account in the PTO's PTA calculation. With regard to the PTO delays before and after the interference, the January 24, 2011 Decision no longer asserts that the Notice mailed August 2, 2001 was a notification under 35 U.S.C. § 132, but still fails to award any PTA for the PTO's delays after the Response filed May 31, 2001 until the interference was declared.

45. On February 17, 2011, within the one month period to respond set forth in the PTO's January 24, 2011 Decision, Plaintiff filed a Request for Reconsideration of Decision on Application for Patent Term Adjustment seeking correction of the PTA award under the

alternative calculations reflected in attached Exhibit A, to a total award of 2729 days or 2730 days PTA. In particular, Plaintiff seeks

(i) an award that takes into account the PTA due under 35 U.S.C. § 154(a)(1)(B), 37 C.F.R. § 1.702(b), and 37 C.F.R. §1.703(b);

(ii) an award that takes into account 663 days PTO delay for the delays associated with the interference, in accordance with 35 U.S.C. § 154(b)(1)(C), 37 C.F.R. §1.703(c)(1), and 37 C.F.R. § 41.205(a);

(iii) an award that takes into account 33 days of PTO delay for the delays associated with failing to grant a patent within four months of the October 1, 2008 issue fee payment, in accordance with 35 U.S.C. § 154(a)(1)(A)(iv), 37 C.F.R. § 1.702(a)(4), and 37 C.F.R. §1.703(a)(6);

(iv) an award that takes into account 2546 days of PTO delay for the PTO's delay beginning on September 30, 2001 (four months after Applicant's May 31, 2001 Response to Restriction Requirement), and ending on the day the Notice of Allowance was issued on September 19, 2008, under 35 U.S.C. § 154(b)(1)(A)(ii), 37 C.F.R. § 1.702(a)(2), and 37 C.F.R. §1.703(a)(2), and as originally determined by the PTO;

(v) in the alternative, if the award does not take into account 2546 days of PTO delay as outlined above, an award that takes into account 366 days of PTO delay for the PTO's delay beginning on September 30, 2001 (four months after Applicant's May 31, 2001 Response to Restriction Requirement), and ending on the day the interference was declared on October 1, 2002, under 35 U.S.C. § 154(b)(1)(A)(ii).

The alternative calculations reflected in attached Exhibit A take into account the periods during which these delays are overlapping, and demonstrate that the '271 patent is entitled to a total PTA award of 2729 days or 2730 days.

IV. TIMELINESS

46. Under 35 U.S.C. § 154(b)(4)(A), "[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after the grant of the patent. Chapter 7 of title 5 shall apply to such action."

47. Under 35 U.S.C. § 154(b)(3)(B)(ii), the Director (Defendant) "shall provide the applicant one opportunity to request reconsideration of any patent term adjustment determination made by the Director."

48. Plaintiff timely requested reconsideration of the PTO's patent term adjustment for the '271 patent on October 22, 2009 , but the PTO did not issue any decision until January 24, 2011, 476 days after the patent issued.

49. Because the PTO did not issue a decision on Plaintiff's request for reconsideration until January 24, 2011, the January 24, 2011 decision could not have been appealed to this Court within the 180-day period set forth in 35 U.S.C. § 154(b)(4)(A).

50. On information and belief, Defendant has a policy of not deciding applications for reconsideration of patent term adjustment filed in accordance with 35 U.S.C. § 154(b)(3) and/or 37 C.F.R. § 1.705 if an applicant files a civil action under 35 U.S.C. § 154(b)(4)(A). Thus, on information and belief, had Plaintiff filed a civil action under 35 U.S.C. § 154(b)(4)(A) within

180 days of the issue date of the '271 patent, the PTO would not have decided Plaintiff's request for reconsideration while an action was pending in this Court, thus depriving Plaintiff of the statutory administrative remedy provided in 35 U.S.C. § 154(b)(3).

V. COUNT ONE: EQUITABLE TOLLING OF 35 U.S.C. § 154(B)(4)(A) AND PATENT TERM ADJUSTMENT UNDER 35 U.S.C § 154

51. The allegations of paragraphs 1-50 are incorporated in this claim for relief as if fully set forth herein.

52. 35 U.S.C. § 154(b)(4)(A) sets a 180 day period for bringing a civil action to challenge a PTO patent term adjustment determination, but it is a non-jurisdictional statute of limitations that should not bar Plaintiff's claims herein.

53. The equitable tolling doctrine is a creation of common law that has been read into statutes of limitations, absent Congressional intent to the contrary.

54. Nothing in 35 U.S.C. § 154 shows Congressional intent to preclude equitable tolling for the 180-day limitations period in 35 U.S.C. § 154(b)(4)(A). To the contrary, by providing for agency review of the PTO determination, *see, e.g.*, 35 U.S.C. § 154(b)(3)(B)(ii), Congress revealed its intention that applicants have the option of allowing the PTO decide patent term adjustment appeals in the first instance. When the PTO does not render a decision within the 180-day limitations period, equitable tolling is necessary to effectuate Congressional intent of allowing applicants an administrative remedy under the patent term adjustment statutory scheme.

55. Plaintiff has been diligently pursing their administrative remedy under 35 U.S.C. § 154. However, the PTO did not render an agency decision until after the 180-day limitations period already had lapsed.

56. Requiring applicants to always file a civil action within the 180-day period in 35 U.S.C. § 154(b)(4)(A) in order to preserve the right to judicial review, even if a request for reconsideration is pending before the PTO, would render the statutory guarantee of an administrative remedy provided in 35 U.S.C. § 154(b)(3)(B)(ii) useless because, on information and belief, the PTO stops all action on a request for reconsideration once a district court civil action is filed. Such a requirement also would needlessly waste judicial resources and raise questions over the Court's jurisdiction to hear an unripe dispute.

57. If the Court determines that Plaintiff may not seek recalculation of the patent term adjustment for the '271 patent under 35 U.S.C. § 154 because it is time barred under 35 U.S.C. § 154(b)(4)(A), Plaintiff will be left with no adequate remedy at law.

58. Requiring the PTO to award patent term adjustment for the '271 patent that provides the full patent term guaranteed under 35 U.S.C. § 154 would not substantially injure any other interested parties because the additional patent term at issue will not take effect until the end of the current term of the '271 patent, which is not set to expire until 2023 under the PTA calculations applied by the PTO. Moreover, the public interest will be furthered by a recalculation of patent term adjustment in a manner that is consistent with 35 U.S.C. § 154.

59. Accordingly, the 180 day limitation period set forth in 35 U.S.C. § 154(b)(4)(A) should be equitably tolled from at least the date Plaintiff filed a request for consideration on October 22, 2009 (16 days after the '271 patent issued) until the PTO first issued a Decision on January 24, 2011.

60. The '271 patent is entitled to a total period of patent term adjustment of 2729 days or 2730 days PTA, as reflected in attached Exhibit A.

VI. COUNT TWO: DECLARATORY JUDGMENT UNDER THE ADMINISTRATIVE PROCEDURE ACT

61. The allegations of paragraphs 1-60 are incorporated in this claim for relief as if fully set forth herein.

62. Defendant's improper calculation of patent term adjustment, including refusing to guarantee the patent term against the PTO delays as set forth herein, was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law within the meaning of 5 U.S.C. § 706(2)(A); contrary to Plaintiff's constitutional rights within the meaning of 5 U.S.C. § 706(2)(B); and in excess of statutory authority within the meaning of 5 U.S.C. § 706(2)(C).

63. Defendant's January 24, 2011 Decision determining patent term adjustment for the '271 patent is believed to be a final agency action that is reviewable under 5 U.S.C. § 704.

64. Plaintiff has filed a Request for Reconsideration of Defendant's January 24, 2011 Decision, but has no assurance that the PTO will render a further decision within any time period that would not prejudice Plaintiff's ability to obtain judicial review. Thus, Plaintiff believes that it effectively has exhausted available administrative remedies.

65. The '271 patent is entitled to a total period of patent term adjustment of 2729 days or 2730 days PTA, as reflected in attached Exhibit A.

VII. COUNT THREE: VIOLATION OF THE FIFTH AMENDMENT OF THE CONSTITUTION OF THE UNITED STATES

66. The allegations of paragraphs 1-65 are incorporated in this claim for relief as if fully set forth herein.

67. The Fifth Amendment of the Constitution of the United States provides in relevant part: "[N]or shall private property be taken for public use, without just compensation."

68. Plaintiff enjoys a substantial and cognizable private property right in the full and complete term of the '271 patent.

69. Plaintiff has paid all necessary maintenance fees owed to date for the '271 patent.

70. Defendant's refusal to award patent term adjustment to compensate for PTO delays as set forth in herein permanently deprived Plaintiff of patent term to which the '271 patent is entitled to under 35 U.S.C. § 154(b).

71. Defendant's purposeful and deliberate diminution of the patent term for the '271 patent constitutes a taking of Plaintiff's property without just compensation in violation of the Fifth Amendment to the Constitution of the United States, requiring recalculation of patent term adjustment to a total period of patent term adjustment of 2729 days or 2730 days PTA, as reflected in attached Exhibit A.

WHEREFORE, Plaintiff respectfully prays that this Court:

A. Issue an Order changing the patent term adjustment for the '271 patent to 2729 days or 2730 days PTA as alternatively calculated in attached Exhibit A;

B. Declare that Defendant's determination of patent term adjustment for the '271 patent is invalid, unconstitutional and contrary to law;

C. Grant such other and further relief as the nature of the case may admit or require, including additional patent term for the '271 patent if further errors are identified and found in the PTO's patent term adjustment calculation methodology, and any such other and further relief as may be deemed just and equitable by this Court.

Dated: March 23, 2011

Respectfully submitted,

Courtenay C. Brinckerhoff
(DC Bar No. 482443)
C. Edward Polk, Jr. (DC Bar No. 472453)

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(202) 672-5300
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Exhibit A

Patent Term Adjustment Calculation System

Add a new event to this case

Docket Number: 091856-0111
Application Number: 09/200743
Patent Number: 7,598,271

	Event Description	Event Date	Days from Filing	PTO Days	Applicant Days
Edit Delete	Application Filing Date	11/27/2000	0		
Edit Delete	Restriction Requirement	04/26/2001	150		
Edit Delete	Restriction Requirement Response Received at PTO	05/31/2001	185		
	Restriction Requirement Response Filed + 4 months	09/30/2001	307		
Edit Delete	IDS NOT falling under 1.704(c)(6), (8) or (10) filed at PTO	03/20/2002	478		
Edit Delete	Interference Declared	10/01/2002	673		
Edit Delete	Interference Decided	05/25/2004	1,275		
Edit Delete	Interference Concluded (60 days after decision)	07/24/2004	1,335	(663)	
	Interference Decided + 4 months	09/25/2004	1,398		
	3 Year Period Starts	09/20/2005	1,758		
Edit Delete	Notice of Allowance	09/19/2008	2,853	(2546),(1455)	
Edit Delete	Issue Fee Paid	10/01/2008	2,865		
	Issue Fee Paid + 4 months	02/01/2009	2,988		
	3 Year Period Stopped	03/05/2009	3,020	(1925)	
Edit Delete	Request for Withdrawal from Issuance	03/06/2009	3,021	(33) 2714	
Edit Delete	Request For Continued Examination (including amendment)	03/06/2009	3,021		
Edit Delete	Notice of Allowance	04/17/2009	3,063		
Edit Delete	Issue Fee Paid	05/21/2009	3,097		
	Issue Fee Paid + 4 months	09/21/2009	3,220		
Edit Delete	Patent Grant Date	10/06/2009	3,235	15	
			Totals:	2,729	0
			PTA:	2,729	

Patent Term Adjustment Calculation System

Application Number: 09/200743
Patent Number: 7,598,271

	Event Description	Event Date	Days from Filing	PTO Days	Applicant Days
	Application Filing Date	11/27/2000	0		
	Restriction Requirement	04/26/2001	150		
	Restriction Requirement Response Received at PTO	05/31/2001	185		
	Restriction Requirement Response Filed + 4 months	09/30/2001	307		
	IDS NOT falling under 1.704(0(6), (8) or (10) filed at PTO	03/20/2002	478		
	Interference Declared	10/01/2002	673	366	
	Interference Decided	05/25/2004	1,275		
	Interference Concluded (60 days after decision)	07/24/2004	1,335	663	
	Interference Decided + 4 months	09/25/2004	1,398		
	3 Year Period Starts	09/20/2005	1,758		
	Notice of Allowance	09/19/2008	2,853	(1455)	
	Issue Fee Paid	10/01/2008	2,865		
	Issue Fee Paid + 4 months	02/01/2009	2,988		
	3 Year Period Stopped	03/05/2009	3,020	(1262)	
	Request for Withdrawal from Issuance	03/06/2009	3,021	(33)1686	
	Request For Continued Examination (including amendment)	03/06/2009	3,021		
	Notice of Allowance	04/17/2009	3,063		
	Issue Fee Paid	05/21/2009	3,097		
	Issue Fee Paid + 4 months	09/21/2009	3,220		
	Patent Grant Date	10/06/2009	3,235	15	
			Totals:	2,730	0
			PTA:	2,730	

Exhibit B

US007598271B1

(12) **United States Patent**
Benneker et al.

(10) **Patent No.: US 7,598,271 B1**
(45) **Date of Patent: Oct. 6, 2009**

(54) **CRYSTALLINE PAROXETINE METHANE SULFONATE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2072 days.

(21) Appl. No.: **09/200,743**

(22) Filed: **Nov. 30, 1998**

Related U.S. Application Data

(62) Division of application No. 08/872,023, filed on Jun. 10, 1997, now Pat. No. 5,874,447.

(51) **Int. Cl.**
A61K 31/445 (2006.01)
C07D 405/12 (2006.01)

(52) **U.S. Cl.** **514/321**; 514/317; 514/319; 546/197; 546/198; 546/205; 546/206; 546/236

(58) **Field of Classification Search** 514/317, 514/319, 321; 546/197, 198, 205, 206, 236
See application file for complete search history.

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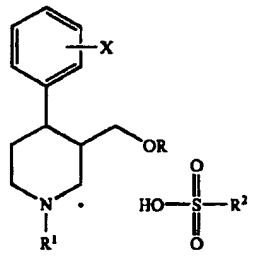
Primary Examiner—Celia Chang
(74) *Attorney, Agent, or Firm*—Foley & Lardner LLP

(57) **ABSTRACT**

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

a nitro group,

hydroxy group,

and/or an alkoxy group.

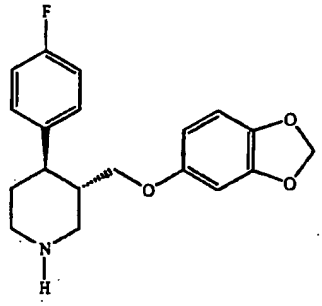
1 Claim, No Drawings

CRYSTALLINE PAROXETINE METHANE SULFONATE

This application is a divisional of prior application Ser. No. 08/872,023, filed Jun. 10, 1997 now U.S. Pat. No. 5,874,447, the entire contents of which are incorporated herein by reference.

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl)piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);
- the hydrated form—a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics, 42, 135-143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

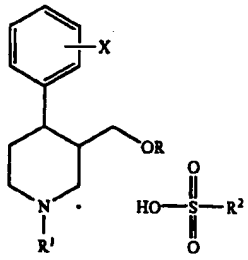
Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the

absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

R^2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

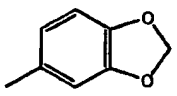
a nitro group,

hydroxy group,

and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

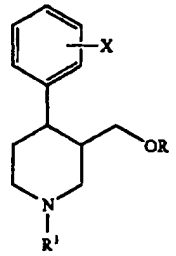


The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1-C4 alkyl group, and most preferably represents a C1-C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20° C. of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

with a sulfonic acid of the general formula R_2—SO_3H,

wherein R_2 represents:

a C1-C10 alkyl group,

a phenyl group optionally substituted by one or more of the following groups:

a C1-C10 alkyl group,

a halogen group,

a nitro group,

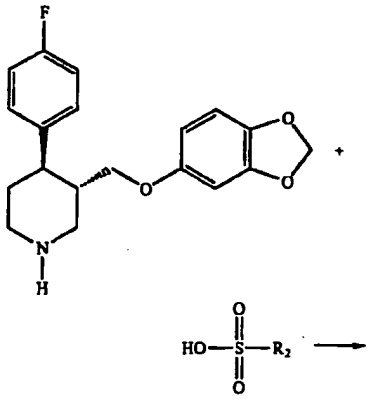
a hydroxy group, and/or

an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:



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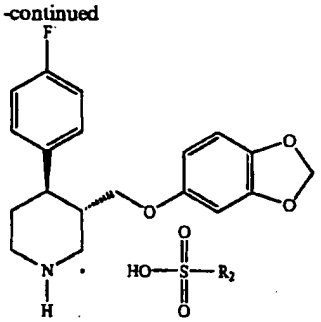
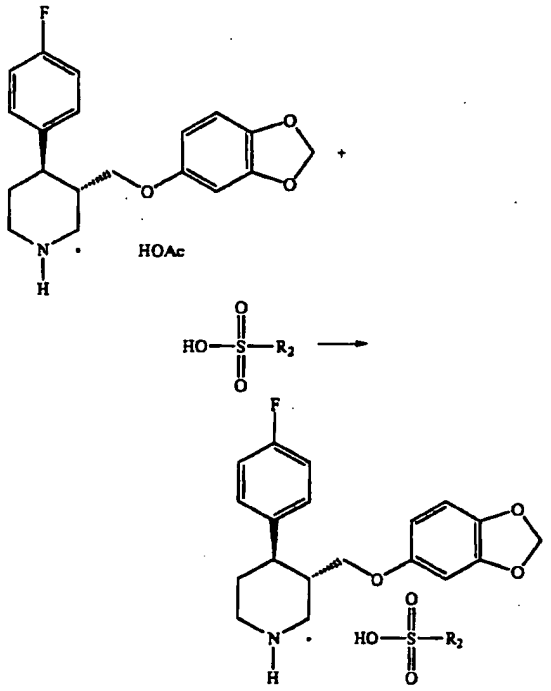


The forming of a solution may preferably proceed at temperatures from about 0° C. to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

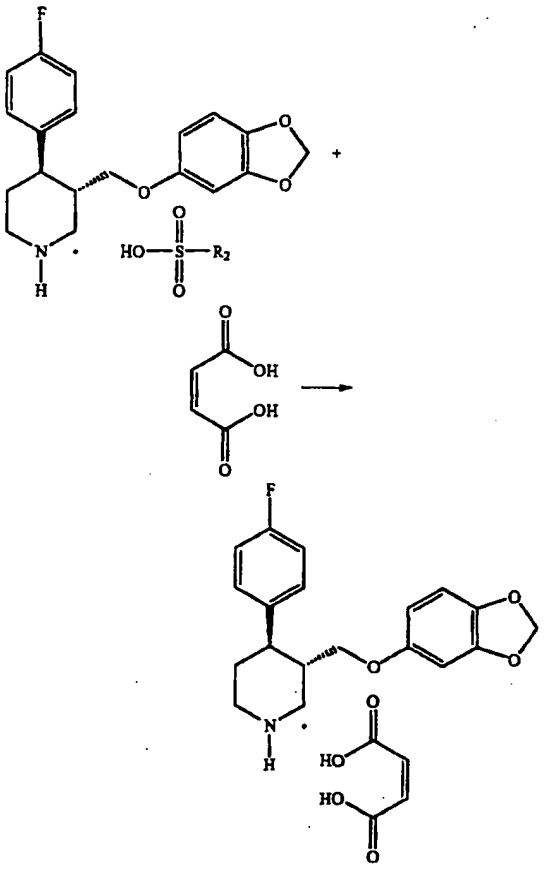


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

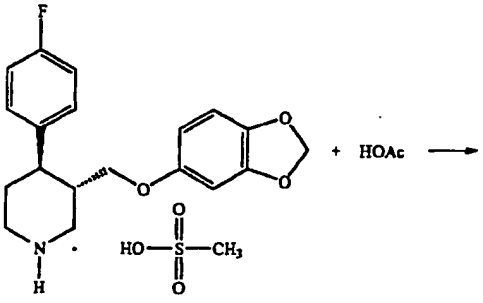
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia,

anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:



and the formation of paroxetine acetate proceeds as follows:



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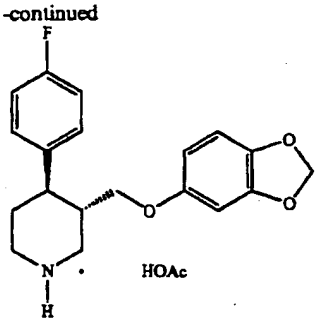
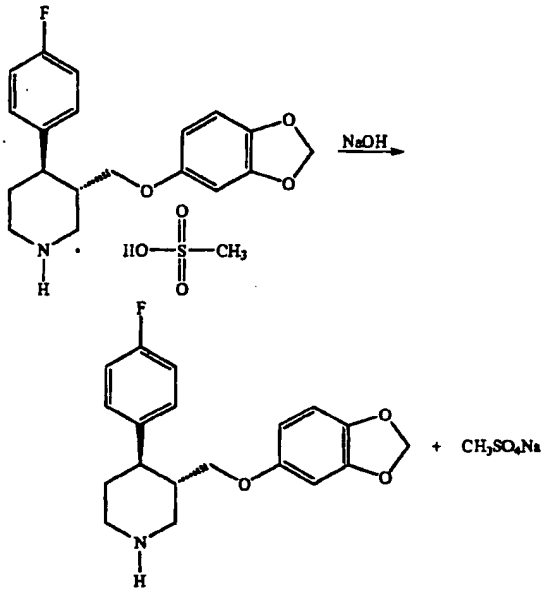


This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate

-continued

hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets, capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g	(8.2 mmol) of paroxetine was dissolved in
15 ml	of hot ethanol.
1.0 g	(10.4 mmol) of methanesulfonic acid in
15 ml	of ethanol was added and the mixture was cooled to room temperature. When the mixture had reached room temperature the mixture was put in the freezer at −20° C. overnight. No crystal line compound was obtained. The mixture was evaporated to dryness leaving an oil. After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in
10 ml	of EtOAc. The waxy crystals were added and the mixture was put in the freezer at −20° C. overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven
2.5 g	(5.9 mmol) of paroxetine methane sulfonate was obtained. Yield 72%

This seeding crystal was subsequently used in following examples 1 and 3.

Examples

Example 1

Paroxetine Methane Sulfonate from Paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in U.S. Pat. No. 4,007,196,

12.7 g	(132 mmol) of methane sulfonic acid was added to
150 ml	of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at −20° C., with a seeding crystal. The obtained solid was filtered off and washed with
50 ml	of ether. The obtained white solid was dried overnight in a vacuumoven.
47.1 g	(111 mmol) of product Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine Benzene Sulfonate from Paroxetine

3.8 g	(11.5 mmol) of paroxetine was dissolved in
10 ml	of hot ethylacetate.
1.82 g	(11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving
5.0 g	(1.3 mmol) of an off white solid. To this solid was added
5 ml	of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.
4.8 g	(9.9 mmol) of product was obtained. Yield 85%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-Toluene Sulfonate from Paroxetine

5.0 g	(15 mmol) of paroxetine was dissolved in
25 ml	of hot ethylacetate.
2.9 g	(15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with

-continued

10 ml	of n-hexane. The obtained white solid was dried overnight in a vacuumoven.
4.8 g	(10 mmol) of a white solid was obtained. Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-Chlorobenzene Sulfonate from Paroxetine

1.1 g	(3.3 mmol) of paroxetine was dissolved in
3 ml	of hot ethylacetate.
0.76 g	(3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with
5 ml	of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving
1.5 g	(2.9 mmol) of an off white solid. Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine Maleate from Paroxetine Methane Sulfonate

1.0 g	(2.4 mmol) of paroxetine methane sulfonate in
5 ml	of hot water. To this solution was added
0.32 g	(2.8 mmol) of maleic acid. The mixture was placed at 4° C. overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with
10 ml	of ether and dried in a vacuumoven.
0.8 g	(2.0 mmol) off white crystals were obtained Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine Acetate from Paroxetine Methane Sulfonate

1.0 g	(2.4 mmol) of paroxetine methane sulfonate in
5 ml	of hot iso-propanol. To this solution was added
0.2 g	(3.2 mmol) of acetic acid. The mixture was placed at 4° C. overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with

-continued

10 ml	of ether and dried in a vacuumoven.
0.5 g	(1.3 mmol) off white crystals were obtained Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine Free Base from Paroxetine Methane Sulfonate

10.0 g	(24.0 mmol) of paroxetine methane sulfonate in
150 ml	of water and
200 ml	of ethyl acetate. To this was added
12.4 g	(31 mmol) of an aqueous 10 wt % NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with
50 ml	of ethyl acetate. The combined organic layers are washed once with
100 ml	of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with
50 ml	of ethyl acetate. The ethyl acetate was evaporated off, leaving
7.5 g	(22.8 mmol) of an oily product. Yield 95%

The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed the results being shown in tables 1-5 below:

TABLE 1

Characterization of salts of paroxetine with certain organic sulfonic acids R—SO_3H

R = CH_3 - (paroxetine methane sulfonate):
m.p.: 142°-144° C.
DSC curve (closed pan, 10° C./min): onset 145.8° C., 79.0 J/g.
IR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99(br d, H_{5ax}, 1H); 2.27(ddd, H_{5eq}, 1H); 2.48-2.65(m, H_3, 1H); 2.82-2.92(m, H_4, CH_3, 4H); 2.95-3.20(m, H_{2ax}, H_{6ax}, 2H); 3.47(dd, H_7, 1H); 3.58-3.74(m, H_{2eq}, H_{6eq}, H_7, 3H); 5.88(s, $H_{7'}$, 2H); 6.10(dd, $H_{6'}$, 1H); 6.33(d, $H_{2'}$, 1H); 6.61(d, $H_{5'}$, 1H); 7.09(dd, $H_{3'}$, $H_{5'}$, 2H); 7.22(dd, $H_{7'}$, $H_{8'}$, 2H); 8.85(br d, NH_{eq}, 1H); 9.11(br d, NH_{ax}, 1H).
13C-NMR(ppm): 30.0(s, C_5); 39.3(s, C_3); 39.5(s, C_4); 41.7(s, SC); 44.6(s, C_6); 46.8(s, C_2); 67.4(s, C_7); 97.8(s, $C_{2'}$); 101.2(s, $C_{7'}$); 105.4(s, $C_{6'}$); 107.8(s, $C_{5'}$); 115.8(d, $C_{3'}$, $C_{5'}$); 128.4(s, $C_{9'}$, $C_{2'}$); 137.1(s, $C_{4'}$); 142.0(s, $C_{1'}$); 148.2(s, $C_{3'}$); 153.7(s, $C_{1'}$); 161.9(d, $C_{4'}$).
R = C_6H_5 - (paroxetine benzene sulfonate):
m.p.: 55°-60° C.
IR spectrum (KBr, in cm^{-1}): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90(br d, H_{5eq}, 1H); 2.10-2.28(m, H_{5ax}, 1H); 2.38-2.52(m, H_3, 1H); 2.82(ddd, H_4, 1H); 3.02-3.18(m, H_{2ax}, H_{6ax}, 2H); 3.37(dd, H_7, 1H); 3.48(d, H_7, 1H); 3.60-3.82(m, H_{2eq}, H_{6eq}, 2H); 5.87(s, $H_{7'}$, 2H); 6.06(dd, $H_{6'}$, 1H); 6.29(d, $H_{2'}$, 1H); 6.60(d, $H_{5'}$, 1H); 6.90(dd, $H_{3'}$, $H_{5'}$, 2H); 7.04(dd, $H_{7'}$, $H_{8'}$, 2H); 7.40(d, ArH, 3H); 7.94(d, SArH, 2H); 8.81(br d, NH_{eq}, 1H); 9.04(br d, NH_{ax} 1H).
13C-NMR (ppm): 29.9(s, C_5); 39.2(s, C_3); 41.5(s, C_4); 4.48(s, C_6); 47.0(s, C_2); 67.3(s, C_7); 97.9(s, $C_{2'}$); 101.2(s, $C_{7'}$); 105.5(s, $C_{6'}$) 107.8(s, $C_{5'}$); 115.7(d, $C_{3'}$, $C_{5'}$); 125.9(s, $C_{9'}$); 128.6(s, $C_{8'}$); 128.8(s, $C_{9'}$, $C_{7'}$); 130.6(s, C_{ar}); 137.1(s, $C_{4'}$); 141.9(s, $C_{1'}$); 144.1(s, C_{ar}); 148.2(s, $C_{3'}$); 153.7(s, $C_{1'}$); 161.8(s, $C_{4'}$).
R = p-$CH_3C_6H_4$ (paroxetine p-toluene sulfonate):
m.p.: 148°-150°C.

TABLE 1-continued

Characterization of salts of paroxetine with certain organic sulfonic acids R—SO_3H

DSC curve (closed pan, 10° C./min): onset 151.6° C., 71.6 J/g.
IR spectrum (KBr, in cm^{-1}): 529, 557, 671, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1186, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89(br d, H_{5eq}, 1H); 2.10-2.50(m, H_{5ax}, H_3, CH_3, 5H); 2.82(ddd, H_4, 1H); 2.97-3.18(m, H_{2ax}, H_{6ax}, 2H); 3.36(dd, H_7, 1H); 3.48(dd, H_7, 1H); 3.52-3.77(m, H_{2eq}, H_{6eq}, 2H); 5.87(s, $H_{7'}$, 2H); 6.06(dd, $H_{6'}$, 1H); 6.28(d, $H_{2'}$, 1H); 6.59(d, $H_{5'}$, 1H); 6.90(dd, H_3, H_5, 2H); 7.05(dd, H_2, H_6, 2H); 7.24(d, CH_3ArH, 2H); 7.83(d, SArH, 2H); 8.91(br d, NH_{eq}, 1H); 9.17(br d, NH_{ax}, 1H).
13C-NMR (ppm): 21.3(s, C_a); 29.9(s, C_5); 39.2(s, C_3); 41.5(s, C_4); 44.7(s, C_6); 46.9(s, C_2); 67.3(s, C_7); 97.8(s, $C_{2'}$); 101.1(s, $C_{7'}$); 105.5(s, $C_{6'}$); 107.8(s, $C_{5'}$); 115.6(d, C_3, C_5); 125.8(s, C_b); 129.0(s, C_g, $C_{7'}$); 129.1(s, C_c); 137.2(s, $C_{4'}$); 140.8(s, C_d); 141.5(s, C_e); 141.9(s, $C_{1'}$); 148.2(s, $C_{3'}$); 153.8(s, $C_{1'}$); 161.8(d, $C_{4'}$).
R = p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate);
m.p.: 75°-80° C.
IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186, 1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029.
1H-NMR (ppm): 1.91(br d, H_{5eq}, 1H); 2.15(ddd, H_{5ax}, 1H); 2.37-2.52(m, H_3, 1H); 2.81(ddd, H_4, 1H); 2.93-3.21(m, H_{2ax}, H_{6ax}, 2H); 3.37(dd, H_7, 1H); 3.49(d, H_7, 1H); 3.61-3.81(m, H_{2eq}, H_{6eq}, 2H); 5.88(s, $H_{7'}$, 2H); 6.05(dd, $H_{6'}$, 1H); 6.27(d, $H_{2'}$, 1H); 6.59(d, $H_{5'}$, 1H); 6.91(dd, H_3, $H_{5'}$, 2H); 7.03(dd, $H_{2'}$, $H_{6'}$, 2H); 7.39(d, ClArH, 2H); 7.86(d, SArH, 2H); 8.78(br d, NH_{eq}, 1H); 9.02(br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0(s, C_5); 39.3(s, C_3); 41.5(s, C_4); 44.9(s, C_6); 47.1(s, C_2); 67.3(s, C_7); 97.9(s, $C_{2'}$); 101.2(s, $C_{7'}$); 105.5(s, $C_{6'}$); 107.9(s, $C_{5'}$); 115.8(d, C_3, C_5); 127.6(s, C_b); 128.8(s, $C_{6'}$, $C_{7'}$); 132.0(s, C_d); 137.0(s, C_e); 137.2(s, $C_{4'}$); 141.8(s, $C_{1'}$); 142.0(s, C_a); 148.2(s, $C_{3'}$); 153.6(s, $C_{1'}$); 161.8(d, $C_{4'}$).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

TABLE 2

Hygroscopicity of certain salts of paroxetine (40° C., 75% rel. hum).

water content (in %) at	t = 0	t = 4 weeks
methane sulfonate	0.35	+0.04
p-toluene sulfonate	0.70	<0.02
hydrochloride	—	+2.5

TABLE 3

Solubility of paroxetine salts in water (in mg/ml)

	20° C.	50° C.
methane sulfonate	>1000/10 min	1300
p-toluene sulfonate	>1000	>1000

TABLE 3-continued

Solubility of paroxetine salts in water (in mg/ml)

	20° C.	50° C.
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

TABLE 4

Stability of paroxetine salts by HPLC (total amount of degradation in %).

	degradation	
	20° C.	80° C.
methane sulfonate	not observed	<0.2%, 3 months
p-toluene sulfonate	not observed	<0.2%, 3 months
maleate	0.2%, 12 months	>50%, 5 days

TABLE 5

Solubility of salts of paroxetine in nonaqueous solvents (in mg/ml)

		methane sulfonate	p-toluene sulfonate
Ethanol	20° C.	36	50
	78° C.	250	>500
2-Propanol	20° C.	7	14
	82° C.	330	>500
Acetone	20° C.	5	16
	56° C.	37	125
Ethyl acetate	20° C.	2	22
	77° C.	25	>500
n-Hexane	20° C.	<0.05	<0.05
	69° C.	0.05	<0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

TABLE 6

Characterization of salts/free base of paroxetine

paroxetine maleate:
m.p.: 128-130° C.
1H-NMR (ppm): 1.65-2.00(m, H_{5eq}, H_{ax}, 2H); 2.00-2.50(m, H_3, 1H); 2.55-3.15(m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15-3.75(m, H_{2eq}, H_{6eq}, H_7, 3H); 5.67(s, $H_{7'}$, 2H); 5.97(s, H_{ar}, 1H); 6.12(dd, $H_{6'}$, 1H); 6.42(d, $H_{2'}$, 1H); 6.67(d, $H_{5'}$, 1H); 6.95-7.35(m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine acetate:
m.p.: 123-125° C.
1H-NMR (ppm): 1.70-2.00(m, H_{5eq}, H_{5ax}, 2H); 1.97(s, H_{ar}, 3H); 2.05-2.50(m, H_3, 1H); 2.50-3.00(m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05-3.75(m, H_{2eq}, H_{6eq}, H_7, 3H); 6.05(s, $H_{7'}$, 2H); 6.28(dd, $H_{6'}$, 1H); 6.58(d, $H_{7'}$, 1H); 6.65(d, $H_{5'}$, 1H); 7.10-7.50(m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine;
1H-NMR (ppm): 1.60-2.00(m, H_{5ax}, H_{5eq}, 2H); 2.00-2.35(m, H_3, 1H); 2.40-2.95(m, H_4, H_{2ax}, H_{6ax}, 3H); 3.15-3.70(m, H_{2eq}, H_{6eq}, H_7, 2H); 5.67(s, $H_{7'}$, 2H); 6.11(dd, $H_{6'}$, 1H); 6.43(d, $H_{2'}$, 1H); 6.62(d, $H_{5'}$, 1H); 6.80-7.35(m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

The invention claimed is:

1. Crystalline paroxetine methanesulfonate having the following IR peaks:

531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.

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